16. (new) The composition of claim 14, wherein the CTL activating peptide is the adenovirus-derived E1A peptide, having the sequence SGPSNTPPEI (SEQ ID NO:2), or the HPV16 E7 peptide derived from human papillomavirus type 16, having the sequence RAHYNIVTF (SEQ ID NO:3).

17. (new) A method of treating a tumor comprising administering to a patient in need of such treatment an anti-CD40 antibody, or a fragment thereof, and a CTL activating peptide which binds to a class I MHC molecule, wherein the anti-CD40 antibody is human, humanized, chimeric or Deimmunised™.

18. (new) A method of treating an infectious disease comprising administering to a patient in need of such treatment an anti-CD40 antibody, or a active fragment thereof, and a CTL activating peptide which binds to the class I MHC molecule, wherein the anti-CD40 antibody is human, humanized, chimeric or Deimmunised™.

19. (new) The method of claim 17 wherein the composition is administered directly to the tumor.

REMARKS

Claims 14-19 are currently pending in this application. Claims 1-13 have been cancelled with no prejudice or disclaimer to the subject matter therein. Applicants reserve the right to file continuation and/or divisional applications directed to the subject matter of claims 1-13. No new matter has been introduced by the addition of these new claims. Support for claims 14-19 may be found in claims 1-7.

I. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-7 have been rejected as lacking enablement for pharmaceutical compositions comprising any CTL activating peptide or the use of said compositions to treat any tumor or infectious disease. Claims 1-7 have been cancelled rendering the rejection moot. This rejection has been rendered moot by the cancellation of these claims and Applicants submit that this rejection should not apply to the new claims.

The Office has alleged that "the specification fails to provide sufficient guidance as to the physical or biological characteristics of peptides other than the E7 peptide having the sequence of SEQ ID NO:3 which are capable of having a therapeutic effect on any disease when administered in vivo in combination with an anti-CD40 antibody." (Office Action at page 4.) The Office states that "there is no guidance concerning the characteristics of CTL activating peptdes, such as length, amino acid composition, hydrophobicity, and stability under physiological conditions." *Id.*

Applicants submit that the following characteristics of CTL activating peptides were common knowledge to persons of ordinary skill in the art at the time the invention was made:

- CTL activating peptides range in length between 8 and 11 amino acids;
- The shape of the antigen-binding groove of a particular class I MHC molecule determines the length and amino acid sequence of the CTL activating peptides that can bind to this MHC molecule;

- The polymorphism between class I MHC molecules is primarily restricted to the antigen binding groove. Consequently, each class I MHC molecule can bind a different set of CTL activating peptides;
- For many class I MHC molecules multiple CTL activating peptides that naturally bind to its groove have been identified. From the sequences of these peptides, algorithms have been derived that can be used to identify additional CTL activating peptides from any protein. Moreover, Algorithms for computer-assisted prediction of CTL activating peptides within any protein sequence are freely available through the internet, for example:

  www.syfpeithi.bmi-heidelberg.com

  www.bimas.dcrt.nih.gov
- The above applies to class I MHC molecules of both mouse and human origin.

Each of the above-mentioned facts has been described in numerous scientific publications, including for example (See attached):

a. Rammensee, H. G., Friede, T., and Stevanoviic, S. MHC ligands and peptide motifs: first listing, Immunogenetics. *41:* 178-228, 1995;

b. Rammensee, H. G. Chemistry of peptides associated with MHC class I and class II molecules, Curr Opin Immunol. *7:* 85-96., 1995;

c. Melief, C. J., Offringa, R., Toes, R. E., and Kast, W. M. Peptide-based cancer vaccines, Curr Opin Immunol. *8:* 651-7., 1996;

d. Ressing, M. E., Offringa, R., Toes, R. E., Ossendorp, F., de Jong, J. H., Brandt, R. M., Kast, W. M., and Melief, C. J. Immunotherapy of cancer by peptide-based vaccines for the induction of tumor-specific T cell immunity, Immunotechnology. *2:* 241-51., 1996.

Moreover, this information can commonly be found in textbooks that are routinely used for student courses in immunology around the world, such as:

a. Immunology 5th Edition, 1998 by Roitt I, Borstoff, J. and Male D., published by Mosby International Ltd., ISBN 0 7234 29189.

b. Immunobiology 4th Edition, 1999 by Janeway C.A., Travers, P., Wa,port, M. and Capra J.D., published by Elsevier Science Ltd./Garland Publishing, ISBN 0 8153 3217 3.

The Office also states that "while the sequences identified as SEQ ID 2 and SEQ ID 3 from E1A and E7, respectively, are derived from viral proteins, the specification does not teach which characteristics of these sequences is responsible for their CTL activating activity.

Methods for identifying or obtaining CTL peptides were commonly known and available to persons of ordinary skill in the art. These include the sequence requirements for generation of such peptides in a cell and for binding to class I MHC molecules. This information can readily be applied for the design of synthetic peptides that represent CTL activating peptides.

Examples of publications concerning this methodology and background are (see attached):

a. D'Amaro, J., Houbiers, J. G., Drijfhout, J. W., Brandt, R. M., Schipper, R., Bavinck, J. N., Melief, C. J., and Kast, W. M. A computer program for predicting possible cytotoxic T lymphocyte epitopes based on HLA class I peptide-binding motifs, Hum Immunol. *43:* 13-8., 1995.
b. Grey, H. M., Ruppert, J., Vitiello, A., Sidney, J., Kast, W. M., Kubo, R. T., and Sette, A. Class I MHC-peptide interactions: structural requirements and functional implications, Cancer Surv. *22:* 37-49, 1995;
c. Uebel, S. and Tampe, R. Specificity of the proteasome and the TAP transporter, Curr Opin Immunol. *11:* 203-8., 1999;
d. Lehner, P. J. and Cresswell, P. Processing and delivery of peptides presented by MHC class I molecules, Curr Opin Immunol. *8:* 59-67., 1996;
e. Groettrup, M., Soza, A., Kuckelkorn, U., and Kloetzel, P. M. Peptide antigen production by the proteasome: complexity provides efficiency, Immunol Today. *17:* 429-35., 1996;
f. Kloetzel, P. M., Soza, A., and Stohwasser, R. The role of the proteasome system and the proteasome activator PA28 complex in the cellular immune response, Biol Chem. *380:* 293-7., 1999;
g. Benham, A. M. and Neefjes, J. J. Antigen processing by the class I pathway, Biochem Soc Trans. *23:* 664-9., 1995;
h. Momburg, F., Neefjes, J. J., and Hammerling, G. J. Peptide selection by MHC-encoded TAP transporters, Curr Opin Immunol. *6:* 32-7., 1994;
i. van der Burg, S. H., Visseren, M. J., Brandt, R. M., Kast, W. M., and Melief, C. J. Immunogenicity of peptides bound to MHC class I molecules depends on the MHC-peptide complex stability, J Immunol. *156:* 3308-14., 1996.

The Office alleges that the issue of identifying or obtaining CTL peptides "is further complicated by the fact that the E1A peptide does not have CTL-activating activity in the absence of anti-CD40."

Applicants submit that it was previously demonstrated that vaccination of mice with the E7 peptide results in effective anti-tumor immunity (Feltkamp et al., Eur J Immunol 23:2242 (1993)), whereas vaccination with the E1A peptide suppresses anti-tumor immunity (Toes et al., PNAS 93: 7855 (1996)). Both publications have been cited in the present specification in examples 3 and 4, respectively. Furthermore, figure 5 of

the present specification demonstrates that the tolerogenic behavior of the E1A peptide is correlated with its capacity to rapidly disperse systemically upon local, subcutaneous injection. Figure 5 also shows that the E7 peptide does not display this behavior.

In example 1 and 2 of the present specification it is described that *in vivo* signaling through CD40 by means of systemic application of agonistic anti-CD40 antibodies results in the *in vivo* activation of bone marrow derived antigen presenting cells (APC). This CD40 signal, which can be derived from either the anti-CD40 antibody or from $CD4^+$ T helper cells, enables the APC to prime CTL immunity. Absence of either of these CD40 signals results in a defect in CTL priming.

The experiments in examples 1 and 2 of the present specification indicate that CD40 triggering *in vivo* through systemic administration of agonistic anti-CD40 antibody can allow CTL priming in the absence of $CD4^+$ T helper cells, a situation in which CTL priming would otherwise not ensue (figure 1b). It was therefore investigated whether a systemic dose of anti-CD40 antibody would similarly allow CTL priming by the systemically dispersed E1A peptide. Indeed, this was found to be the case (figures 6 and 7).

The Office further states that "the two CTL activating peptides described by the specification each comprise a single MHC class I epitope. The potential immune response to vaccination with a single MHC class I epitope is limited to a CTL response as the epitopes described do not bind to MHC class II. "

Indeed, class I MHC binding peptides generally do not bind to class II MHC molecules. Consequently, treatment with class I MHC binding peptides is generally limited to the induction of class I MHC-restricted $CD8^+$ CTL immunity, and does not result in the induction of class II MHC-restricted $CD4^+$ T helper responses. These principles are described in the textbooks cited above and should therefore be considered as common knowledge among persons of ordinary skill in the art. Similarly, the skilled artisan is well aware that treatment with class I MHC binding CTL activating peptides does not generally induce antibodies capable of recognizing the protein from which this peptide has been derived. Accordingly, the description of the present specification stresses the point that the application of anti-CD40 antibodies is restricted to the induction of CTL immunity. No mention was made of anti-CD40 antibodies for the induction of $CD4^+$ T helper or antibody immune responses.

The Office also alleged that "the specification does not specifically identify any infectious diseases which can be treated using the instant methods or identify infections which can be successfully treated by generating a CTL response alone. "

Applicants assert that it was commonly known to persons of ordinary skill in the art that CTL-mediated immunity plays a major role in eliminating cells that are infected by any of the majority of pathogenic agents (see textbooks mentioned above). Therefore, Applicants assert that an increase in CTL immunity results in improved clearance of the majority of infectious agents.

Further, the Office has alleged that "the specification does not provide sufficient guidance as to the affects of the route of administration on CTL generation or demonstrate that injection of peptide and anti-CD4O either systemically or locally at any site in the body can generate therapeutic CTL activity."

It is clear to the skilled artisan from the present description that the formulation consists of two components:

- a CTL activating peptide which upon injection becomes loaded into the class I MHC molecules of antigens presenting cells; and
- an agonistic anti-CD40 antibody capable of binding to the CD40 molecule of bone marrow derived antigen presenting cells and, thereupon, activating this antigen presenting cell.

Furthermore, it is clear to the skilled artisan from the present description that a given antigen presenting cell is capable of priming a given CTL immune response if:

- the class I MHC molecules at the surface of the antigen presenting cell are loaded with the appropriate CTL activating peptides
- while at the same time the antigen presenting cell has been properly activated through receiving a stimulatory signal through its CD40 receptor.

Therefore, the present description allows persons of ordinary skill in the art to recognize that co-localization of the CTL activating peptide and the agonistic anti-CD40 antibody is enhance priming of CTL immunity against the CTL activating peptide. This implies that both peptide and anti-CD40 antibody can be administered in such a manner that they are both delivered systemically, or both locally at the same site (e.g. at the site of tumor growth).

In addition, it is commonly known to persons of ordinary skill in the art that the capacity of infectious agents or tumors to evade destruction by CTL immunity may depend both on the sensitivity of the infected cells or tumor cells to CTL, as well as on the magnitude of the CTL response. The present specification embodies a methodology for increasing the magnitude of the CTL response against a given CTL activating peptide and, as such, for decreasing the likelihood that infectious agents or tumors comprising this CTL activating peptide can evade destruction by CTL immunity. It cannot be concluded that failure of CTL immunity induced by protocols described by Yasutomi et al. implicates the failure of CTL immunity induced by the clearly distinct methodology described in the present specification.

Conclusion

In view of the foregoing amendments and remarks, Applicants request timely allowance of the pending claims.

The Applicants request that the Examiner contact the undersigned at (713) 578-4182 to discuss any additional amendments necessary to place the claims in condition for allowance.

Respectfully Submitted,

Dated: March 11, 2002.

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